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Incidence and Outcomes Associated With *Clostridium difficile* Infections

A Systematic Review and Meta-analysis

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Key Points

Question

What is the incidence of hospital-onset *Clostridium difficile* infection (CDI) and its associated length of stay?

Findings

This systematic review and meta-analysis of 13 studies using patient-days as the denominator found that the incidence of hospital-onset CDI was 8.3 cases per 10 000 patient-days. Among propensity score–matched studies of the length of stay, the mean difference in length of stay between patients with and those without CDI varied from 3.0 to 21.6 days.

Meaning

Pooled estimates from currently available literature suggest that CDI is associated with a large burden on the US health care system.

Abstract

Importance

An understanding of the incidence and outcomes of *Clostridium difficile* infection (CDI) in the United States can inform investments in prevention and treatment interventions.

Objective

To quantify the incidence of CDI and its associated hospital length of stay (LOS) in the United States using a systematic literature review and meta-analysis.

Data Sources

MEDLINE via Ovid, Cochrane Library Databases via Wiley, Cumulative Index of Nursing and Allied Health Complete via EBSCO Information Services, Scopus, and Web of Science were searched for studies published in the United States between 2000 and 2019 that evaluated CDI and its associated LOS.

Study Selection

Incidence data were collected only from multicenter studies that had at least 5 sites. The LOS studies were included only if they assessed postinfection LOS or used methods accounting for time to infection using a multistate model or compared propensity score–matched patients with CDI with control patients without CDI. Long-term-care facility studies were excluded. Of the 119 full-text articles, 86 studies (72.3%) met the selection criteria.

Data Extraction and Synthesis

Two independent reviewers performed the data abstraction and quality assessment. Incidence data were pooled only when the denominators used the same units (eg, patient-days). These data were pooled by summing the number of hospital-onset CDI incident cases and the denominators across studies. Random-effects models were used to obtain pooled mean differences. Heterogeneity was assessed using the I^2 value. Data analysis was performed in February 2019.

Main Outcomes and Measures

Incidence of CDI and CDI-associated hospital LOS in the United States.

Results

When the 13 studies that evaluated incidence data in patient-days due to hospital-onset CDI were pooled, the CDI incidence rate was 8.3 cases per 10 000 patient-days. Among propensity score–matched studies (16 of 20 studies), the CDI-associated mean difference in LOS (in days) between patients with and without CDI varied from 3.0 days (95% CI, 1.44-4.63 days) to 21.6 days (95% CI, 19.29-23.90 days).

Conclusions and Relevance

Pooled estimates from currently available literature suggest that CDI is associated with a large burden on the health care system. However, these estimates should be interpreted with caution because higher-quality studies should be completed to guide future evaluations of CDI prevention and treatment interventions.

Introduction

Clostridium difficile (also known as *Clostridioides difficile*) is the most common pathogen causing health care–associated infections in the United States, accounting for 15% of all such infections.[1] A Centers for Disease Control and Prevention report on antibiotic resistance threats categorized *C difficile* as an urgent threat.[2] Antibiotic treatment for *C difficile* infection (CDI) is often followed by recurrent infection, leading

to nontraditional treatments, such as fecal transplant and oral administration of nontoxigenic *C difficile* spores.[3,4]

Information about the burden of CDI in the United States could inform investments in prevention and treatment interventions. This information should include the incidence of CDI, how this incidence has changed over time, and poor outcomes associated with CDI. Although prior studies have shown that CDI is associated with poor outcomes, such as recurrence, long hospital length of stay (LOS), mortality, and high treatment costs, these results vary by study location and patient population.[2,5] In addition, many current estimates of the poor outcomes and costs associated with CDI do not take into account the underlying severity of illness among patients who develop CDI and may overestimate the true attributable outcomes.[6]

To address gaps in our understanding of the current burden associated with CDI in the United States, we conducted a systematic literature review of studies conducted in the United States and published after 2000 that evaluated the incidence of CDI and associated LOS. The goals were to describe the recent incidence of CDI and to evaluate LOS attributable to CDI.

Methods

Search Strategy

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)[7] and Meta-analysis of Observational Studies in Epidemiology (MOOSE)[8] reporting guidelines. An experienced health sciences librarian (A.B.) conducted systematic searches in MEDLINE via Ovid, Cochrane Library Databases via Wiley, Cumulative Index of Nursing and Allied Health Complete via EBSCO Information Services, Scopus, and Web of Science to identify articles published from the inception of the database to February 2019. Citations published before 2000 were excluded. A combination of keywords and subject headings were used for "*Clostridium difficile*," "length of stay," and "incidence." The full search strategies can be found in eAppendix 1 in the Supplement.

Inclusion and Exclusion Criteria

Publications were included if they evaluated the incidence of CDI or LOS associated with CDI. Studies were excluded if they did not contain original data, did not have a control group, were published outside the United States, were published in a language other than English, or were published before 2000. The year 2000 was chosen as the beginning of this systematic literature review because that was when the epidemic BI/NAP1/027 strain of *C difficile* emerged, after which CDI increased in prevalence and became less responsive to treatment.[4] We excluded studies if they assessed only a specific subset of patients, unless that population could be categorized as 1 of the following subsets: immunocompromised patients, patients in the intensive care unit, patients with cancer, patients with end-stage renal disease, patients undergoing hemodialysis, surgical patients, solid-organ transplant recipients, patients with high-risk gastrointestinal conditions, or peripartum women. We excluded studies with a study period of less than 1 year. We also excluded studies of long-term care facilities. Incidence data were collected only from multicenter studies that had at least 5 sites, because single-site or small studies may be biased by outbreaks or other local conditions. We included incidence studies with denominators of patient-days or person-years, known timing of the CDI such as after surgery or after admission (ie, hospital onset [HO]), or exclusion of patients with a history of CDI.

Studies were included in the LOS analysis only if they provided data on postinfection LOS, if they used methods accounting for time to infection using a multistate model, or if propensity score–matched patients with CDI were compared with uninfected controls.[5,9] Studies were excluded if they did not have an

uninfected control group or a denominator that included patients without CDI.

Data Extraction and Quality Assessment

Titles and abstracts of all articles were screened to assess inclusion criteria. Two of 9 independent reviewers (M.L.S., M.A.W., M.F.K., H.-Y.C., M.L.C., L.A.H., D.J.D., A.R.M., and E.N.P.) abstracted data for each article. Reviewers resolved disagreements by consensus.

The reviewers abstracted data on study design, study population, setting and years, inclusion and exclusion criteria, number of patients included, description of control group, definition of CDI, outcomes (eg, incidence and LOS), and an assessment of the potential risk of bias. Risk of bias was assessed using the Downs and Black scale.[10] Reviewers followed all questions from this scale as written except for question 27 (a single item on the Power subscale, which was scored 0-5), which was changed to a yes or no. Two of us (A.R.M. and M.L.S.) performed component quality analysis independently, reviewed all inconsistent assessments, and resolved disagreements by consensus.[11]

Statistical Analysis

Data analysis was performed in February 2019. Excel spreadsheet software version 2007 (Microsoft Corp) and RevMan statistical software version 5.3 (Cochrane Community) were used for statistical analysis. Incidence data were pooled only when the denominators used the same units (eg, patient-days). These data were pooled by summing the number of HO-CDI incident cases and the denominators across studies. Pooled incidence was reported as the number of incident cases per the given denominator (eg, 10 000 patient-days).[12] No *P* values were calculated.

Results

Of the 34 775 articles identified (Figure), 119 were full-text articles, and 86 (72.3%) of those articles met the selection criteria and were included in the systematic literature review.[13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93] Among these, 66 articles evaluated incidence,[13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78] and 20 articles evaluated LOS.[16,54,66,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95] One-fifth of the studies that assessed LOS (4 studies)[84,87,91,94] scored 18 or more points of the 28 points possible on the Downs and Black scale[10] and, thus, were considered to be of higher quality.

Incidence of CDI Calculated Using Patient-Days (13 Studies)

Sixty-six studies[13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78] measured CDI incidence. Thirteen of those 66 studies[13,14,15,16,17,18,19,20,21,22,23,24,25] used patient-days as the denominator (Table 1). Among these studies, the CDI incidence varied from 2.8 CDI cases per 10 000 patient-days[22] to 15.8 CDI cases per 10 000 patient-days.[20] Three studies[13,17,23] were conducted by the Centers for Disease Control and Prevention. Three studies[17,18,21] were done in New York State. One study[24] from Southern California found that the incidence of community-onset, health care facility (HCF)–associated CDI (11.1 cases per 10 000 patient-days) was almost 2-fold higher than that for HO, HCF-associated CDI (6.8 cases per 10 000 patient-days). The pooled incidence of HO-CDI among the 13 studies[13,14,15,16,17,18,19,20,21,22,23,24,25] (Table 1) that used patient-days as the denominator was 8.3 CDI

cases per 10 000 patient-days. Four studies[13,15,18,21] included more than 100 facilities.

The definitions of *C difficile* used to identify cases varied. Three studies[17,18,21] used clinical findings and results of laboratory tests for *C difficile*, 3 studies[13,14,23] used the Centers for Disease Control and Prevention surveillance definition to identify *C difficile*, 2 studies[20,22] applied infection preventionist evaluations for *C difficile* surveillance, and 2 studies[24,25] used only results of laboratory tests for *C difficile*. The remaining studies used a variety of ways to identify CDI, including *International Classification of Diseases, Ninth Revision* (*ICD-9*) codes or other billing codes,[15,16,19] laboratory test results,[15,16,20,23] clinical findings,[15,23] and initial doses of *C difficile* antibiotic therapy.[19] When we examined incidence by time period, we found that the early studies from 2000 to 2008 had a range from 2.8 to 12.2 CDI cases per 10 000 patient-days, studies from 2008 to 2009 had a range from 6.3 to 9.6 CDI cases per 10 000 patient-days, and the later studies after 2010 reported a range from 6.8 to 15.8 CDI cases per 10 000 patient-days (Table 1).

Incidence of CDI Calculated Using Person-Years (17 Studies)

Fourteen studies[26,27,28,29,30,31,32,33,34,35,36,37,38,39] included both inpatients and outpatients (Table 2), reflected in a denominator of person-years in 8 studies.[27,28,29,30,32,34,36,39] Seven of those 14 studies[27,28,29,30,32,34,39] used only *ICD-9* codes to define CDI. In a study[36] of adult and adolescent patients with HIV/AIDS that included more than 100 hospitals, during 10 years of study, the peak incidence of CDI was 9.59 cases per 1000 person-years among patients with clinical AIDS. A study[28] of the Armed Forces Health Surveillance Center in Maryland over the course of 12 years found the incidence of community-associated CDI to be 5.5 cases per 100 000 person-years. In a study[29] evaluating the annual incidence of CDI and multiply recurrent CDI per 1000 person-years, the incidences increased by 42.7% and 188.8%, respectively, during a decade (2001-2012) in the United States. In another study[30] with 12 years of data from 5 administrative databases, elderly people (ie, aged >65 years) had a CDI rate of 677 cases per 100 000 person-years. In contrast, a managed-care organization in Colorado found that the CDI incidence in 2007 was 14.9 CDI cases per 10 000 patient-years.[32] These studies were too diverse to pool together into 1 estimate.

Three studies[40,41,42] included only inpatients (Table 2). Two of these studies[41,42] assessed the Agency for Healthcare Research and Quality (AHRQ) National Inpatient Sample (NIS). One evaluated infant patients from the AHRQ NIS cohort,[41] and the other study evaluated adult patients from the AHRQ NIS cohort.[42] Both studies documented substantial increases in CDI incidence between 2000 and 2005, from 2.8 to 5.1 cases per 10 000 hospitalizations, and from 5.5 to 11.2 cases per 10 000 hospitalizations, respectively.[41,42] The third study,[40] which was from the US National Hospital Discharge Survey between 2001 and 2010, found that the incidence of CDI in the pediatric population was 1.2 CDI discharges per 1000 total discharges.

Incident Cases of CDI (36 Studies)

Twenty-six studies[43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68] documented HO-CDIs, which we assumed were incident cases (Table 3). Of these studies, the AHRQ NIS was the main data set, represented by 10 included studies.[43,45,47,50,51,56,58,59,61,68] These studies assessed diverse patient populations with different comorbidities, including peripartum women[68] and patients with inflammatory bowel disease,[43] lymphoma,[45] leukemia,[58] subarachnoid hemorrhage treated with microsurgical or endovascular aneurysm repair,[47] chronic liver disease,[50] hematopoietic stem cell transplant,[51] megacolon,[56] or heart failure.[59] Thus, the results of these studies were also too diverse to pool together. One study[68] found that the CDI incidence among peripartum women increased from 0.36 cases per 10 000 in 1998 to 0.70 cases per 10 000 in 2006. The US National Hospital Discharge Survey database was

represented in 6 included studies.[49,52,53,55,64,65] These studies also assessed diverse patient populations, including children[52] and adults with different comorbidities, such as cancer[49,52] and inflammatory bowel disease.[65] In 1 of these studies,[65] the overall incidence of HO-CDI was 369.8 cases per 10 000 hospitalizations for inflammatory bowel disease. In that same study,[65] the HO-CDI incidence was 445.6 cases per 10 000 hospitalizations for ulcerative colitis and 220.3 cases per 10 000 hospitalizations for Crohn disease.

Ten studies[69,70,71,72,73,74,75,76,77,78] evaluated surgical patients (Table 3), and, thus, we assumed that the CDI cases were incident cases. Five studies[73,75,76,77,78] used data from AHRQ NIS. These AHRQ NIS studies analyzed a variety of surgical procedures, including spine surgery[76]; hip,[73] knee,[77] or lower-extremity[78] arthroplasty; and elective colon resections.[75] One of them had CDI occurring in 1.4% of patients, for a rate of 144.99 cases of *C difficile* colitis per 10 000 elective colon resections, and the incidence increased from 1.31% in 2004 to 1.67% in 2006.[75]

LOS Associated With CDI (20 Studies)

Twenty studies[16,54,66,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94] (Table 4) evaluated CDI-associated LOS. Sixteen studies[54,66,79,80,81,82,83,84,85,86,87,88,89,92,94,95] used propensity score matching to evaluate LOS associated with CDI, 2 studies[16,93] used postinfection LOS, 1 study[90] matched on LOS from admission until either positive *C difficile* test results or discharge, and 1 study[91] accounted for time to infection using a multistate model. Also, one of the propensity score matched–studies applied multistate modeling to account for timing of infection.[88] Pediatric patients were included in 3 of these studies.[66,86,87]

Among the 13 propensity score–matched studies of adults, the CDI-associated mean difference in LOS (in days) between patients with CDI and patients who did not have CDI varied greatly from 3.0 days (95% CI, 1.44-4.63 days)[79] to 10.3 days.[54] Among the 3 pediatric propensity score–matched studies,[66,86,87] the highest CDI-associated mean difference in LOS (in days) was 21.6 days (95% CI, 19.29-23.90 days).[66]

Among the studies that used multistate models to account for timing of infection, a study[91] performed in the Veterans Affairs health care system found that the magnitude of its estimated impact was smaller when methods were used to account for the time-varying nature of infection. That study estimated a CDI-attributable LOS of only 2.27 days (95% CI, 2.14-2.40 days).[91] The other study[88] that performed propensity score matching and used a multistate model converged on similar excess LOS estimates of 3.1 days (95% CI, 1.7-4.4 days) and 3.3 days (95% CI, 2.6-4.0 days), respectively.

Four studies[84,87,91,94] that evaluated LOS earned 18 or more points on the Downs and Black scale.[10] One study[91] also used multistate modeling. Another was also performed in the Veterans Affairs health care system[84,91] and found a mean difference between patients with and without CDI of 7.5 days.[84] One study[87] of pediatric patients found that those with CDI had a longer LOS (adjusted odds ratio, 4.34; 95% CI, 3.97-4.83). Another study[94] of adult patients in Pennsylvania hospitals showed an attributable hospital LOS difference of 2.4 days (95% CI, 0.7-4.4 days; $P < .01$) between patients with and without CDI.

Discussion

National epidemiological investigations have demonstrated recent marked increases in CDI in the United States.[34] Thus, a national public health response to this increase requires current estimates of the CDI incidence.[96,97,98] Our systematic review of the literature found that the CDI incidence varied by study and that the investigators used different denominators when they calculated the incidence for specific study populations. In our meta-analysis of studies that used patient-days as the denominator, we estimated the incidence of CDI in the United States to be 8.3 CDI cases per 10 000 patient-days.

Variation in CDI incidence may be due, in part, to advances in diagnostic technology and variations in diagnostic practices.[99,100,101] Nucleic acid amplification tests are more sensitive than traditional *C difficile* stool tests (eg, toxin enzyme immunoassay). Nucleic acid amplification tests have been used more frequently in clinical practice since 2009, when the first commercial polymerase chain reaction was approved by the US Food and Drug Administration.[102] The topic of CDI testing methods and risk adjustment is complex.[103,104] Concerns have been expressed about the adequacy of risk adjustment to account for different CDI testing methods (toxin enzyme immunoassay alone, polymerase chain reaction alone, toxin enzyme immunoassay plus glutamate dehydrogenase followed by polymerase chain reaction for discrepancies, polymerase chain reaction followed by toxin enzyme immunoassay, and other diagnostic options) across HCFs. The choice of testing methods substantially affects the performance of these testing algorithms.[99,100,101]

In addition, the CDI incidence found by these studies likely varied because of the different database structures adopted by the various hospitals.[13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78] Some analyses were based on health care systems databases, but most used large infection control surveillance, state, or national discharge databases.[13,14,15,16,17,18,19,20,21,22,23,24,25] Beginning in January 2013, the Centers for Medicare & Medicaid Services began requiring public reporting of CDI rates via the National Healthcare Safety Network for those hospitals participating in the Inpatient Prospective Payment System.[64] Specifically, 1 study[29] demonstrated an increase in the annual incidence of CDI and multiply recurrent CDI per 1000 person-years by 42.7% and 188.8%, respectively, between 2001 and 2012. Another CDI surveillance study[33] in 7 US states reported an increase not only in community-associated CDI incidence rates but also an increase in health care–associated CDI incidence rates. Furthermore, CDI can complicate comorbid conditions and result in the need for additional hospital resources.[34] Included studies detected an increase in the CDI incidence in patients with inflammatory bowel disease,[43] patients with cancer,[52] those undergoing surgery,[75,76] and even infants.[41] The results of our systematic review of literature and meta-analysis emphasize the need to perform *C difficile* surveillance and direct resources to the prevention of CDI in order to reduce the incidence across the United States.

Limitations

This systematic literature review has some limitations. First, the results of systematic literature reviews and meta-analyses are only as valid as the results of the studies evaluated. Most studies included in this systematic literature review were of moderate-to-low quality and may have overestimated the outcomes. We need more high-quality studies so that we can accurately determine postinfection LOS, because LOS before the infection should not be attributed to *C difficile*.[5] Second, we included studies that used *ICD-9* codes to define CDI. The *ICD-9* codes are used for billing purposes and are not ideal for surveillance. However, a prior meta-analysis[105] found that the *ICD-9* code for *C difficile* had good sensitivity, specificity, positive predictive value, and negative predictive value compared with clinical definitions. Third, we only included studies conducted in the United States and published in English, which limits the external validity of this research. We used these inclusion criteria because our goal was to evaluate the burden of CDI in the United States. Future systematic literature reviews should be performed to evaluate this burden in other countries. Fourth, we found heterogeneity in all LOS-stratified analyses (eAppendix 2 and eTable in the Supplement). We found that the higher-quality studies that used advanced statistical methods to attempt to account for time-dependent bias found lower CDI-attributable LOS compared with other studies that did not use advanced methods. In addition, our incidence estimates were derived from multicenter studies only. Incidence rates in small studies may be variable and subject to bias; thus, this criterion was established a priori to determine representative incidence rates. From incident cases of CDI

(36 studies), we were unable to exclude recurrent and multiply recurrent CDI cases if the study did not exclude those cases. For this meta-analysis, we decided to calculate the incidence rate with studies with a similar denominator (patient-days), with a result of 8.3 CDI cases per 10 000 patient-days.

Conclusions

Pooled estimates from the currently available literature suggest that *C difficile* is associated with a large burden on the US health care system. However, these estimates should be used with caution, and higher-quality studies should be completed to guide future evaluations of *C difficile* prevention and treatment interventions.

Notes

Supplement.

eAppendix 1. Search Methods

eAppendix 2. Statistical Methods

eReferences.

eTable. Subset Analyses Evaluating Hospital Length of Stay Attributable to *Clostridium difficile* Infection (8 Studies)

References

1. Magill SS, O'Leary E, Janelle SJ, et al. ; Emerging Infections Program Hospital Prevalence Survey Team . Changes in prevalence of health care-associated infections in U.S. hospitals. N Engl J Med. 2018;379(18):-. doi:10.1056/NEJMoa1801550 [PubMed: 30380384] [CrossRef: 10.1056/NEJMoa1801550]

2. Centers for Disease Control and Prevention Antibiotic resistance threats in the United States, 2013. https://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf. Published April 23, 2013. Accessed November 7, 2019.

3. Gerding DN, Meyer T, Lee C, et al. Administration of spores of nontoxigenic *Clostridium difficile* strain M3 for prevention of recurrent *C. difficile* infection: a randomized clinical trial. JAMA. 2015;313(17):1719-1727. doi:10.1001/jama.2015.3725 [PubMed: 25942722] [CrossRef: 10.1001/jama.2015.3725]

4. Bagdasarian N, Rao K, Malani PN. Diagnosis and treatment of *Clostridium difficile* in adults: a systematic review. JAMA. 2015;313(4):398-408. doi:10.1001/jama.2014.17103 [PMCID: PMC6561347] [PubMed: 25626036] [CrossRef: 10.1001/jama.2014.17103]

5. Zhang S, Palazuelos-Munoz S, Balsells EM, Nair H, Chit A, Kyaw MH. Cost of hospital management of *Clostridium difficile* infection in United States: a meta-analysis and modelling study. BMC Infect Dis. 2016;16(1):447. doi:10.1186/s12879-016-1786-6 [PMCID: PMC5000548] [PubMed: 27562241] [CrossRef: 10.1186/s12879-016-1786-6]

6. Nelson RE, Nelson SD, Khader K, et al. The magnitude of time-dependent bias in the estimation of excess length of stay attributable to healthcare-associated infections. Infect Control Hosp Epidemiol. 2015;36(9):1089-1094. doi:10.1017/ice.2015.129 [PubMed: 26041436] [CrossRef: 10.1017/ice.2015.129]

7. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009;339:b2700. doi:10.1136/bmj.b2700 [PMCID: PMC2714672] [PubMed: 19622552] [CrossRef: 10.1136/bmj.b2700]

8. Stroup DF, Berlin JA, Morton SC, et al. ; Meta-analysis of Observational Studies in Epidemiology (MOOSE) Group . Meta-analysis of observational studies in epidemiology: a proposal for reporting. JAMA. 2000;283(15):2008-2012. doi:10.1001/jama.283.15.2008 [PubMed: 10789670] [CrossRef: 10.1001/jama.283.15.2008]

9. van Kleef E, Green N, Goldenberg SD, et al. Excess length of stay and mortality due to *Clostridium difficile* infection: a multi-state modelling approach. J Hosp Infect. 2014;88(4):213-217. doi:10.1016/j.jhin.2014.08.008 [PubMed: 25441017] [CrossRef: 10.1016/j.jhin.2014.08.008]

10. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health. 1998;52(6):377-384. doi:10.1136/jech.52.6.377 [PMCID: PMC1756728] [PubMed: 9764259] [CrossRef: 10.1136/jech.52.6.377]

11. Alderson PGS, Higgins JPT. Assessment of Study Quality: Cochrane Reviewer's Handbook 4.2.3. Chichester, UK: John Wiley & Sons, Ltd; 2004.

12. Chan KY, Wang W, Wu JJ, et al. ; Global Health Epidemiology Reference Group (GHERG) Epidemiology of Alzheimer's disease and other forms of dementia in China, 1990-2010: a systematic review and analysis. Lancet. 2013;381(9882):2016-2023. doi:10.1016/S0140-6736(13)60221-4 [PubMed: 23746902] [CrossRef: 10.1016/S0140-6736(13)60221-4]

13. Archibald LK, Banerjee SN, Jarvis WR. Secular trends in hospital-acquired *Clostridium difficile* disease in the United States, 1987-2001. J Infect Dis. 2004;189(9):1585-1589. doi:10.1086/383045 [PubMed: 15116293] [CrossRef: 10.1086/383045]

14. Burger T, Fry D, Fusco R, et al. Multihospital surveillance of nosocomial methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococcus, and *Clostridium difficile*: analysis of a 4-year data-sharing project, 1999-2002. Am J Infect Control. 2006;34(7):458-464. doi:10.1016/j.ajic.2005.08.010 [PubMed: 16945694] [CrossRef: 10.1016/j.ajic.2005.08.010]

15. Campbell RJ, Giljahn L, Machesky K, et al. *Clostridium difficile* infection in Ohio hospitals and nursing homes during 2006. Infect Control Hosp Epidemiol. 2009;30(6):526-533. doi:10.1086/597507 [PubMed: 19419272] [CrossRef: 10.1086/597507]

16. Dubberke ER, Butler AM, Yokoe DS, et al. Multicenter study of *Clostridium difficile* infection rates from 2000 to 2006. Infect Control Hosp Epidemiol. 2010;31(10):1030-1037. doi:10.1086/656245 [PMCID: PMC3648217] [PubMed: 20695799] [CrossRef: 10.1086/656245]

17. Gase KA, Haley VB, Xiong K, Van Antwerpen C, Stricof RL. Comparison of 2 *Clostridium difficile* surveillance methods: National Healthcare Safety Network's laboratory-identified event reporting module versus clinical infection surveillance. Infect Control Hosp Epidemiol. 2013;34(3):284-290. doi:10.1086/669509 [PubMed: 23388363] [CrossRef: 10.1086/669509]

18. Haley VB, DiRienzo AG, Lutterloh EC, Stricof RL. Quantifying sources of bias in National Healthcare Safety Network laboratory-identified *Clostridium difficile* infection rates. Infect Control Hosp Epidemiol. 2014;35(1):1-7. doi:10.1086/674389 [PubMed: 24334790] [CrossRef: 10.1086/674389]

19. Kim J, Smathers SA, Prasad P, Leckerman KH, Coffin S, Zaoutis T. Epidemiological features of

Clostridium difficile-associated disease among inpatients at children's hospitals in the United States, 2001-2006. Pediatrics. 2008;122(6):1266-1270. doi:10.1542/peds.2008-0469 [PubMed: 19047244] [CrossRef: 10.1542/peds.2008-0469]

20. Kamboj M, Son C, Cantu S, et al. Hospital-onset *Clostridium difficile* infection rates in persons with cancer or hematopoietic stem cell transplant: a C3IC network report. Infect Control Hosp Epidemiol. 2012;33(11):1162-1165. doi:10.1086/668023 [PMCID: PMC3670420] [PubMed: 23041818] [CrossRef: 10.1086/668023]

21. McDonald LC, Lessa F, Sievert D, et al. ; Centers for Disease Control and Prevention (CDC) Vital signs: preventing *Clostridium difficile* infections. MMWR Morb Mortal Wkly Rep. 2012;61(9):157-162. [PubMed: 22398844]

22. Miller BA, Chen LF, Sexton DJ, Anderson DJ. Comparison of the burdens of hospital-onset, healthcare facility-associated *Clostridium difficile* infection and of healthcare-associated infection due to methicillin-resistant *Staphylococcus aureus* in community hospitals. Infect Control Hosp Epidemiol. 2011;32(4):387-390. doi:10.1086/659156 [PubMed: 21460491] [CrossRef: 10.1086/659156]

23. Sohn S, Climo M, Diekema D, et al. ; Prevention Epicenter Hospitals . Varying rates of *Clostridium difficile*-associated diarrhea at prevention epicenter hospitals. Infect Control Hosp Epidemiol. 2005;26(8):676-679. doi:10.1086/502601 [PubMed: 16156322] [CrossRef: 10.1086/502601]

24. Tartof SY, Yu KC, Wei R, Tseng HF, Jacobsen SJ, Rieg GK. Incidence of polymerase chain reaction-diagnosed *Clostridium difficile* in a large high-risk cohort, 2011-2012. Mayo Clin Proc. 2014;89(9):1229-1238. doi:10.1016/j.mayocp.2014.04.027 [PubMed: 25064782] [CrossRef: 10.1016/j.mayocp.2014.04.027]

25. Zilberberg MD, Tabak YP, Sievert DM, et al. Using electronic health information to risk-stratify rates of *Clostridium difficile* infection in US hospitals. Infect Control Hosp Epidemiol. 2011;32(7):649-655. doi:10.1086/660360 [PubMed: 21666394] [CrossRef: 10.1086/660360]

26. Chernak E, Johnson CC, Weltman A, et al. Severe *Clostridium difficile*–associated disease in populations previously at low risk: four states, 2005. https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5447a1.htm. Published December 2, 2005. Accessed November 7, 2019.

27. Dubberke ER, Olsen MA, Stwalley D, et al. Identification of Medicare recipients at highest risk for *Clostridium difficile* infection in the US by population attributable risk analysis. PLoS One. 2016;11(2):e0146822. doi:10.1371/journal.pone.0146822 [PMCID: PMC4747338] [PubMed: 26859403] [CrossRef: 10.1371/journal.pone.0146822]

28. Gutiérrez RL, Riddle MS, Porter CK. Epidemiology of *Clostridium difficile* infection among active duty United States military personnel (1998-2010). BMC Infect Dis. 2013;13:609. doi:10.1186/1471-2334-13-609 [PMCID: PMC3880161] [PubMed: 24373384] [CrossRef: 10.1186/1471-2334-13-609]

29. Ma GK, Brensinger CM, Wu Q, Lewis JD. Increasing incidence of multiply recurrent *Clostridium difficile* infection in the United States: a cohort study. Ann Intern Med. 2017;167(3):152-158. doi:10.7326/M16-2733 [PubMed: 28672282] [CrossRef: 10.7326/M16-2733]

30. Olsen MA, Young-Xu Y, Stwalley D, et al. The burden of *Clostridium difficile* infection: estimates of the incidence of CDI from U.S. Administrative databases. BMC Infect Dis. 2016;16:177. doi:10.1186/s12879-016-1501-7 [PMCID: PMC4840985] [PubMed: 27102582] [CrossRef: 10.1186/s12879-016-1501-7]

31. Rabatsky-Ehr T, Purviance K, Mlynarski D, Mshar P, Hadler J, Sosa L. Surveillance for community-associated *Clostridium difficile*: Connecticut, 2006. https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5713a3.htm. Published April 4, 2008. Accessed November 7, 2019.

32. Kuntz JL, Johnson ES, Raebel MA, et al. *Clostridium difficile* infection, Colorado and the northwestern United States, 2007. Emerg Infect Dis. 2012;18(6):960-962. doi:10.3201/eid1806.111528 [PMCID: PMC3358157] [PubMed: 22608207] [CrossRef: 10.3201/eid1806.111528]

33. Lessa FC, Mu Y, Winston LG, et al. Determinants of *Clostridium difficile* infection incidence across diverse United States geographic locations. Open Forum Infect Dis. 2014;1(2):ofu048. doi:10.1093/ofid/ofu048 [PMCID: PMC4281776] [PubMed: 25734120] [CrossRef: 10.1093/ofid/ofu048]

34. Reveles KR, Lawson KA, Mortensen EM, et al. National epidemiology of initial and recurrent *Clostridium difficile* infection in the Veterans Health Administration from 2003 to 2014. PLoS One. 2017;12(12):e0189227. doi:10.1371/journal.pone.0189227 [PMCID: PMC5720754] [PubMed: 29216276] [CrossRef: 10.1371/journal.pone.0189227]

35. Rhee SM, Tsay R, Nelson DS, van Wijngaarden E, Dumyati G. *Clostridium difficile* in the pediatric population of Monroe County, New York. J Pediatric Infect Dis Soc. 2014;3(3):183-188. doi:10.1093/jpids/pit091 [PubMed: 26625381] [CrossRef: 10.1093/jpids/pit091]

36. Sanchez TH, Brooks JT, Sullivan PS, et al. ; Adult/Adolescent Spectrum of HIV Disease Study Group . Bacterial diarrhea in persons with HIV infection, United States, 1992-2002. Clin Infect Dis. 2005;41(11):1621-1627. doi:10.1086/498027 [PubMed: 16267735] [CrossRef: 10.1086/498027]

37. Troppy TS, Mishra T, Barton K, et al. Using public health surveillance data to measure *Clostridium difficile* infection population burden in Massachusetts. Am J Infect Control. 2019;47(2):211-212. doi:10.1016/j.ajic.2018.08.009 [PubMed: 30301654] [CrossRef: 10.1016/j.ajic.2018.08.009]

38. Wendt JM, Cohen JA, Mu Y, et al. *Clostridium difficile* infection among children across diverse US geographic locations. Pediatrics. 2014;133(4):651-658. doi:10.1542/peds.2013-3049 [PubMed: 24590748] [CrossRef: 10.1542/peds.2013-3049]

39. Young-Xu Y, Kuntz JL, Gerding DN, et al. *Clostridium difficile* infection among Veterans Health Administration patients. Infect Control Hosp Epidemiol. 2015;36(9):1038-1045. doi:10.1017/ice.2015.138 [PubMed: 26047207] [CrossRef: 10.1017/ice.2015.138]

40. Argamany JR, Aitken SL, Lee GC, Boyd NK, Reveles KR. Regional and seasonal variation in *Clostridium difficile* infections among hospitalized patients in the United States, 2001-2010. Am J Infect Control. 2015;43(5):435-440. doi:10.1016/j.ajic.2014.11.018 [PubMed: 25952045] [CrossRef: 10.1016/j.ajic.2014.11.018]

41. Zilberberg MD, Shorr AF, Kollef MH. Increase in *Clostridium difficile*-related hospitalizations among infants in the United States, 2000-2005. Pediatr Infect Dis J. 2008;27(12):1111-1113. doi:10.1097/INF.0b013e31817eef13 [PubMed: 19068517] [CrossRef: 10.1097/INF.0b013e31817eef13]

42. Zilberberg MD, Shorr AF, Kollef MH. Increase in adult *Clostridium difficile*-related hospitalizations and case-fatality rate, United States, 2000-2005. Emerg Infect Dis. 2008;14(6):929-931. doi:10.3201/eid1406.071447 [PMCID: PMC2600276] [PubMed: 18507904] [CrossRef: 10.3201/eid1406.071447]

43. Barber GE, Hendler S, Okafor P, Limsui D, Limketkai BN. Rising incidence of intestinal infections in inflammatory bowel disease: a nationwide analysis. Inflamm Bowel Dis. 2018;24(8):1849-1856. doi:10.1093/ibd/izy086 [PubMed: 29722832] [CrossRef: 10.1093/ibd/izy086]

44. Barlam TF, Soria-Saucedo R, Ameli O, Cabral HJ, Kaplan WA, Kazis LE. Retrospective analysis of long-term gastrointestinal symptoms after *Clostridium difficile* infection in a nonelderly cohort. PLoS One. 2018;13(12):e0209152. doi:10.1371/journal.pone.0209152 [PMCID: PMC6296708] [PubMed: 30557401] [CrossRef: 10.1371/journal.pone.0209152]

45. Bhandari S, Pandey RK, Dahal S, et al. Risk, outcomes, and predictors of *Clostridium difficile* infection in lymphoma: a nationwide study. South Med J. 2018;111(10):628-633. doi:10.14423/SMJ.0000000000000872 [PubMed: 30285271] [CrossRef: 10.14423/SMJ.0000000000000872]

46. Brown KA, Daneman N, Jones M, et al. The drivers of acute and long-term care *Clostridium difficile* infection rates: a retrospective multilevel cohort study of 251 facilities. Clin Infect Dis. 2017;65(8):1282-1288. doi:10.1093/cid/cix532 [PubMed: 28595289] [CrossRef: 10.1093/cid/cix532]

47. Dasenbrock HH, Bartolozzi AR, Gormley WB, Frerichs KU, Aziz-Sultan MA, Du R. *Clostridium difficile* infection after subarachnoid hemorrhage: a nationwide analysis. Neurosurgery. 2016;78(3):412-420. doi:10.1227/NEU.0000000000001065 [PubMed: 26485334] [CrossRef: 10.1227/NEU.0000000000001065]

48. Davis ML, Sparrow HG, Ikwuagwu JO, Musick WL, Garey KW, Perez KK. Multicentre derivation and validation of a simple predictive index for healthcare-associated *Clostridium difficile* infection. Clin Microbiol Infect. 2018;24(11):1190-1194. doi:10.1016/j.cmi.2018.02.013 [PubMed: 29454848] [CrossRef: 10.1016/j.cmi.2018.02.013]

49. Delgado A, Reveles IA, Cabello FT, Reveles KR. Poorer outcomes among cancer patients diagnosed with *Clostridium difficile* infections in United States community hospitals. BMC Infect Dis. 2017;17(1):448. doi:10.1186/s12879-017-2553-z [PMCID: PMC5481960] [PubMed: 28645266] [CrossRef: 10.1186/s12879-017-2553-z]

50. Dotson KM, Aitken SL, Sofjan AK, Shah DN, Aparasu RR, Garey KW. Outcomes associated with *Clostridium difficile* infection in patients with chronic liver disease. Epidemiol Infect. 2018;146(9):1101-1105. doi:10.1017/S0950268818001036 [PMCID: PMC6057822] [PubMed: 29739486] [CrossRef: 10.1017/S0950268818001036]

51. Guddati AK, Kumar G, Ahmed S, et al. Incidence and outcomes of *Clostridium difficile*-associated disease in hematopoietic cell transplant recipients. Int J Hematol. 2014;99(6):758-765. doi:10.1007/s12185-014-1577-z [PubMed: 24715522] [CrossRef: 10.1007/s12185-014-1577-z]

52. Gupta A, Pardi DS, Baddour LM, Khanna S. Outcomes in children with *Clostridium difficile* infection: results from a nationwide survey. Gastroenterol Rep (Oxf). 2016;4(4):293-298. [PMCID: PMC5193063] [PubMed: 27081152]

53. Gupta A, Tariq R, Frank RD, et al. Trends in the incidence and outcomes of hospitalized cancer patients with *Clostridium difficile* infection: a nationwide analysis. J Natl Compr Canc Netw. 2017;15(4):466-472. doi:10.6004/jnccn.2017.0046 [PubMed: 28404757] [CrossRef: 10.6004/jnccn.2017.0046]

54. Jiang Y, Viner-Brown S, Baier R. Burden of hospital-onset *Clostridium difficile* infection in patients discharged from Rhode Island hospitals, 2010-2011: application of present on admission indicators. Infect Control Hosp Epidemiol. 2013;34(7):700-708. doi:10.1086/670993 [PubMed: 23739074] [CrossRef: 10.1086/670993]

55. Khanna S, Gupta A, Baddour LM, Pardi DS. Epidemiology, outcomes, and predictors of mortality in hospitalized adults with *Clostridium difficile* infection. Intern Emerg Med. 2016;11(5):657-665. doi:10.1007/s11739-015-1366-6 [PubMed: 26694494] [CrossRef: 10.1007/s11739-015-1366-6]

56. Kuy S, Jenkins P, Romero RA, Samra N, Kuy S. Increasing incidence of and increased mortality associated with *Clostridium difficile*-associated megacolon. JAMA Surg. 2016;151(1):85-86. doi:10.1001/jamasurg.2015.2677 [PubMed: 26445319] [CrossRef: 10.1001/jamasurg.2015.2677]

57. Lessa FC, Mu Y, Bamberg WM, et al. Burden of *Clostridium difficile* infection in the United States. N Engl J Med. 2015;372(9):825-834. doi:10.1056/NEJMoa1408913 [PubMed: 25714160] [CrossRef: 10.1056/NEJMoa1408913]

58. Luo R, Greenberg A, Stone CD. Outcomes of *Clostridium difficile* infection in hospitalized leukemia patients: a nationwide analysis. Infect Control Hosp Epidemiol. 2015;36(7):794-801. doi:10.1017/ice.2015.54 [PubMed: 25801085] [CrossRef: 10.1017/ice.2015.54]

59. Mamic P, Heidenreich PA, Hedlin H, Tennakoon L, Staudenmayer KL. Hospitalized patients with heart failure and common bacterial infections: a nationwide analysis of concomitant *Clostridium difficile* infection rates and in-hospital mortality. J Card Fail. 2016;22(11):891-900. doi:10.1016/j.cardfail.2016.06.005 [PubMed: 27317844] [CrossRef: 10.1016/j.cardfail.2016.06.005]

60. Miller AC, Polgreen LA, Cavanaugh JE, Polgreen PM. Hospital *Clostridium difficile* infection (CDI) incidence as a risk factor for hospital-associated CDI. Am J Infect Control. 2016;44(7):825-829. doi:10.1016/j.ajic.2016.01.006 [PMCID: PMC5040340] [PubMed: 26944007] [CrossRef: 10.1016/j.ajic.2016.01.006]

61. Miller AC, Polgreen LA, Cavanaugh JE, Polgreen PM. Hospital *Clostridium difficile* infection rates and prediction of length of stay in patients without *C. difficile* infection. Infect Control Hosp Epidemiol. 2016;37(4):404-410. doi:10.1017/ice.2015.340 [PMCID: PMC5037957] [PubMed: 26858126] [CrossRef: 10.1017/ice.2015.340]

62. Pant C, Deshpande A, Gilroy R, Olyaee M, Donskey CJ. Rising incidence of *Clostridium difficile* related discharges among hospitalized children in the United States. Infect Control Hosp Epidemiol. 2016;37(1):104-106. doi:10.1017/ice.2015.234 [PubMed: 26424193] [CrossRef: 10.1017/ice.2015.234]

63. Pant C, Deshpande A, Desai M, et al. Outcomes of *Clostridium difficile* infection in pediatric solid organ transplant recipients. Transpl Infect Dis. 2016;18(1):31-36. doi:10.1111/tid.12477 [PubMed: 26538348] [CrossRef: 10.1111/tid.12477]

64. Reveles KR, Lee GC, Boyd NK, Frei CR. The rise in *Clostridium difficile* infection incidence among hospitalized adults in the United States: 2001-2010. Am J Infect Control. 2014;42(10):1028-1032. doi:10.1016/j.ajic.2014.06.011 [PubMed: 25278388] [CrossRef: 10.1016/j.ajic.2014.06.011]

65. Saffouri G, Gupta A, Loftus EV Jr, Baddour LM, Pardi DS, Khanna S. The incidence and outcomes from *Clostridium difficile* infection in hospitalized adults with inflammatory bowel disease. Scand J Gastroenterol. 2017;52(11):1240-1247. doi:10.1080/00365521.2017.1362466 [PubMed: 28782372] [CrossRef: 10.1080/00365521.2017.1362466]

66. Sammons JS, Localio R, Xiao R, Coffin SE, Zaoutis T. *Clostridium difficile* infection is associated with increased risk of death and prolonged hospitalization in children. Clin Infect Dis. 2013;57(1):1-8. doi:10.1093/cid/cit155 [PMCID: PMC3669523] [PubMed: 23532470] [CrossRef: 10.1093/cid/cit155]

67. Murphy CR, Avery TR, Dubberke ER, Huang SS. Frequent hospital readmissions for *Clostridium difficile* infection and the impact on estimates of hospital-associated *C. difficile* burden. Infect Control Hosp Epidemiol. 2012;33(1):20-28. doi:10.1086/663209 [PMCID: PMC3657466] [PubMed: 22173518] [CrossRef: 10.1086/663209]

68. Kuntz JL, Yang M, Cavanaugh J, Saftlas AF, Polgreen PM. Trends in *Clostridium difficile* infection

among peripartum women. Infect Control Hosp Epidemiol. 2010;31(5):532-534. doi:10.1086/652454 [PubMed: 20350150] [CrossRef: 10.1086/652454]

69. Aquina CT, Probst CP, Becerra AZ, et al. High variability in nosocomial *Clostridium difficile* infection rates across hospitals after colorectal resection. Dis Colon Rectum. 2016;59(4):323-331. doi:10.1097/DCR.0000000000000539 [PubMed: 26953991] [CrossRef: 10.1097/DCR.0000000000000539]

70. Bovonratwet P, Bohl DD, Russo GS, Ondeck NT, Singh K, Grauer JN. Incidence, risk factors, and impact of *Clostridium difficile* colitis after spine surgery. Spine (Phila Pa 1976). 2018;43(12):861-868. doi:10.1097/BRS.0000000000002430 [PubMed: 28953711] [CrossRef: 10.1097/BRS.0000000000002430]

71. Bovonratwet P, Bohl DD, Russo GS, et al. How common—and how serious—is *Clostridium difficile* colitis after geriatric hip fracture? findings from the NSQIP dataset. Clin Orthop Relat Res. 2018;476(3):453-462. doi:10.1007/s11999.0000000000000099 [PMCID: PMC6260047] [PubMed: 29443839] [CrossRef: 10.1007/s11999.0000000000000099]

72. Bovonratwet P, Bohl DD, Malpani R, Nam D, Della Valle CJ, Grauer JN. Incidence, risk factors, and impact of *Clostridium difficile* colitis following primary total hip and knee arthroplasty. J Arthroplasty. 2018;33(1):205-210. doi:10.1016/j.arth.2017.08.004 [PubMed: 28870746] [CrossRef: 10.1016/j.arth.2017.08.004]

73. Delanois RE, George NE, Etcheson JI, Gwam CU, Mistry JB, Mont MA. Risk factors and costs associated with *Clostridium difficile* colitis in patients with prosthetic joint infection undergoing revision total hip arthroplasty. J Arthroplasty. 2018;33(5):1534-1538. doi:10.1016/j.arth.2017.11.035 [PubMed: 29273290] [CrossRef: 10.1016/j.arth.2017.11.035]

74. Englesbe MJ, Brooks L, Kubus J, et al. A statewide assessment of surgical site infection following colectomy: the role of oral antibiotics. Ann Surg. 2010;252(3):514-519. doi:10.1097/SLA.0b013e3181f244f8 [PMCID: PMC2997819] [PubMed: 20739852] [CrossRef: 10.1097/SLA.0b013e3181f244f8]

75. Lesperance K, Causey MW, Spencer M, Steele SR. The morbidity of *Clostridium difficile* infection after elective colonic resection: results from a national population database. Am J Surg. 2011;201(2):141-148. doi:10.1016/j.amjsurg.2010.09.017 [PubMed: 21266214] [CrossRef: 10.1016/j.amjsurg.2010.09.017]

76. Guzman JZ, Skovrlj B, Rothenberg ES, et al. The burden of *Clostridium difficile* after cervical spine surgery. Global Spine J. 2016;6(4):314-321. doi:10.1055/s-0035-1562933 [PMCID: PMC4868580] [PubMed: 27190732] [CrossRef: 10.1055/s-0035-1562933]

77. Gwam CU, George NE, Etcheson JI, et al. *Clostridium difficile* infection in the USA: incidence and associated factors in revision total knee arthroplasty patients. Eur J Orthop Surg Traumatol. 2019;29(3):667-674. doi:10.1007/s00590-018-2319-3 [PubMed: 30350019] [CrossRef: 10.1007/s00590-018-2319-3]

78. Maltenfort MG, Rasouli MR, Morrison TA, Parvizi J. *Clostridium difficile* colitis in patients undergoing lower-extremity arthroplasty: rare infection with major impact. Clin Orthop Relat Res. 2013;471(10):3178-3185. doi:10.1007/s11999-013-2906-x [PMCID: PMC3773117] [PubMed: 23479237] [CrossRef: 10.1007/s11999-013-2906-x]

79. Campbell R, Dean B, Nathanson B, Haidar T, Strauss M, Thomas S. Length of stay and hospital costs among high-risk patients with hospital-origin *Clostridium difficile*-associated diarrhea. J Med Econ. 2013;16(3):440-448. doi:10.3111/13696998.2013.770749 [PubMed: 23356421] [CrossRef:

10.3111/13696998.2013.770749]

80. Drozd EM, Inocencio TJ, Braithwaite S, et al. Mortality, hospital costs, payments, and readmissions associated with *Clostridium difficile* infection among Medicare beneficiaries. Infect Dis Clin Pract (Baltim Md). 2015;23(6):318-323. doi:10.1097/IPC.0000000000000299 [PMCID: PMC5102274] [PubMed: 27885315] [CrossRef: 10.1097/IPC.0000000000000299]

81. Dubberke ER, Butler AM, Reske KA, et al. Attributable outcomes of endemic *Clostridium difficile*-associated disease in nonsurgical patients. Emerg Infect Dis. 2008;14(7):1031-1038. doi:10.3201/eid1407.070867 [PMCID: PMC2600322] [PubMed: 18598621] [CrossRef: 10.3201/eid1407.070867]

82. Egorova NN, Siracuse JJ, McKinsey JF, Nowygrod R. Trend, risk factors, and costs of *Clostridium difficile* infections in vascular surgery. Ann Vasc Surg. 2015;29(4):792-800. doi:10.1016/j.avsg.2014.10.031 [PubMed: 25595110] [CrossRef: 10.1016/j.avsg.2014.10.031]

83. Gabriel V, Grigorian A, Phillips JL, et al. A propensity score analysis of *Clostridium difficile* infection among adult trauma patients. Surg Infect (Larchmt). 2018;19(7):661-666. doi:10.1089/sur.2018.110 [PubMed: 30204556] [CrossRef: 10.1089/sur.2018.110]

84. Li X, Wilson M, Nylander W, Smith T, Lynn M, Gunnar W. Analysis of morbidity and mortality outcomes in postoperative *Clostridium difficile* infection in the Veterans Health Administration. JAMA Surg. 2016;151(4):314-322. doi:10.1001/jamasurg.2015.4263 [PubMed: 26606675] [CrossRef: 10.1001/jamasurg.2015.4263]

85. Magee G, Strauss ME, Thomas SM, Brown H, Baumer D, Broderick KC. Impact of *Clostridium difficile*-associated diarrhea on acute care length of stay, hospital costs, and readmission: a multicenter retrospective study of inpatients, 2009-2011. Am J Infect Control. 2015;43(11):1148-1153. doi:10.1016/j.ajic.2015.06.004 [PubMed: 26521932] [CrossRef: 10.1016/j.ajic.2015.06.004]

86. Mehrotra P, Jang J, Gidengil C, Sandora TJ. Attributable cost of *Clostridium difficile* infection in pediatric patients. Infect Control Hosp Epidemiol. 2017;38(12):1472-1477. doi:10.1017/ice.2017.240 [PubMed: 29173236] [CrossRef: 10.1017/ice.2017.240]

87. Nylund CM, Goudie A, Garza JM, Fairbrother G, Cohen MB. *Clostridium difficile* infection in hospitalized children in the United States. Arch Pediatr Adolesc Med. 2011;165(5):451-457. doi:10.1001/archpediatrics.2010.282 [PMCID: PMC4683604] [PubMed: 21199971] [CrossRef: 10.1001/archpediatrics.2010.282]

88. Pak TR, Chacko KI, O'Donnell T, et al. Estimating local costs associated with *Clostridium difficile* infection using machine learning and electronic medical records. Infect Control Hosp Epidemiol. 2017;38(12):1478-1486. doi:10.1017/ice.2017.214 [PMCID: PMC5923033] [PubMed: 29103378] [CrossRef: 10.1017/ice.2017.214]

89. Radcliff TA, Lorden AL, Zhao H. *Clostridium difficile* infection in Texas Hospitals, 2007-2011. Infect Control Hosp Epidemiol. 2016;37(3):357-359. doi:10.1017/ice.2015.291 [PubMed: 26651237] [CrossRef: 10.1017/ice.2015.291]

90. Song X, Bartlett JG, Speck K, Naegeli A, Carroll K, Perl TM. Rising economic impact of *Clostridium difficile*-associated disease in adult hospitalized patient population. Infect Control Hosp Epidemiol. 2008;29(9):823-828. doi:10.1086/588756 [PubMed: 18643746] [CrossRef: 10.1086/588756]

91. Stevens VW, Khader K, Nelson RE, et al. Excess length of stay attributable to *Clostridium difficile* infection (CDI) in the acute care setting: a multistate model. Infect Control Hosp Epidemiol.

2015;36(9):1024-1030. doi:10.1017/ice.2015.132 [PubMed: 26006153] [CrossRef: 10.1017/ice.2015.132]

92. Stewart DB, Hollenbeak CS. *Clostridium difficile* colitis: factors associated with outcome and assessment of mortality at a national level. J Gastrointest Surg. 2011;15(9):1548-1555. doi:10.1007/s11605-011-1615-6 [PubMed: 21720924] [CrossRef: 10.1007/s11605-011-1615-6]

93. Stewart DB, Yacoub E, Zhu J. Chemotherapy patients with *C. difficile* colitis have outcomes similar to immunocompetent *C. difficile* patients. J Gastrointest Surg. 2012;16(8):1566-1572. doi:10.1007/s11605-012-1930-6 [PubMed: 22692587] [CrossRef: 10.1007/s11605-012-1930-6]

94. Tabak YP, Zilberberg MD, Johannes RS, Sun X, McDonald LC. Attributable burden of hospital-onset *Clostridium difficile* infection: a propensity score matching study. Infect Control Hosp Epidemiol. 2013;34(6):588-596. doi:10.1086/670621 [PubMed: 23651889] [CrossRef: 10.1086/670621]

95. Zilberberg MD, Nathanson BH, Sadigov S, Higgins TL, Kollef MH, Shorr AF. Epidemiology and outcomes of *Clostridium difficile*-associated disease among patients on prolonged acute mechanical ventilation. Chest. 2009;136(3):752-758. doi:10.1378/chest.09-0596 [PubMed: 19465510] [CrossRef: 10.1378/chest.09-0596]

96. Shah DN, Aitken SL, Barragan LF, et al. Economic burden of primary compared with recurrent *Clostridium difficile* infection in hospitalized patients: a prospective cohort study. J Hosp Infect. 2016;93(3):286-289. doi:10.1016/j.jhin.2016.04.004 [PubMed: 27209056] [CrossRef: 10.1016/j.jhin.2016.04.004]

97. Shorr AF, Zilberberg MD, Wang L, Baser O, Yu H. Mortality and costs in *Clostridium difficile* infection among the elderly in the United States. Infect Control Hosp Epidemiol. 2016;37(11):1331-1336. doi:10.1017/ice.2016.188 [PubMed: 27572289] [CrossRef: 10.1017/ice.2016.188]

98. Gabriel L, Beriot-Mathiot A. Hospitalization stay and costs attributable to *Clostridium difficile* infection: a critical review. J Hosp Infect. 2014;88(1):12-21. doi:10.1016/j.jhin.2014.04.011 [PubMed: 24996516] [CrossRef: 10.1016/j.jhin.2014.04.011]

99. Polage CR, Gyorke CE, Kennedy MA, et al. Overdiagnosis of *Clostridium difficile* infection in the molecular test era. JAMA Intern Med. 2015;175(11):1792-1801. doi:10.1001/jamainternmed.2015.4114 [PMCID: PMC4948649] [PubMed: 26348734] [CrossRef: 10.1001/jamainternmed.2015.4114]

100. Moehring RW, Lofgren ET, Anderson DJ. Impact of change to molecular testing for *Clostridium difficile* infection on healthcare facility-associated incidence rates. Infect Control Hosp Epidemiol. 2013;34(10):1055-1061. doi:10.1086/673144 [PMCID: PMC3967243] [PubMed: 24018922] [CrossRef: 10.1086/673144]

101. Planche TD, Davies KA, Coen PG, et al. Differences in outcome according to *Clostridium difficile* testing method: a prospective multicentre diagnostic validation study of *C difficile* infection. Lancet Infect Dis. 2013;13(11):936-945. doi:10.1016/S1473-3099(13)70200-7 [PMCID: PMC3822406] [PubMed: 24007915] [CrossRef: 10.1016/S1473-3099(13)70200-7]

102. Burnham CA, Carroll KC. Diagnosis of *Clostridium difficile* infection: an ongoing conundrum for clinicians and for clinical laboratories. Clin Microbiol Rev. 2013;26(3):604-630. doi:10.1128/CMR.00016-13 [PMCID: PMC3719497] [PubMed: 23824374] [CrossRef: 10.1128/CMR.00016-13]

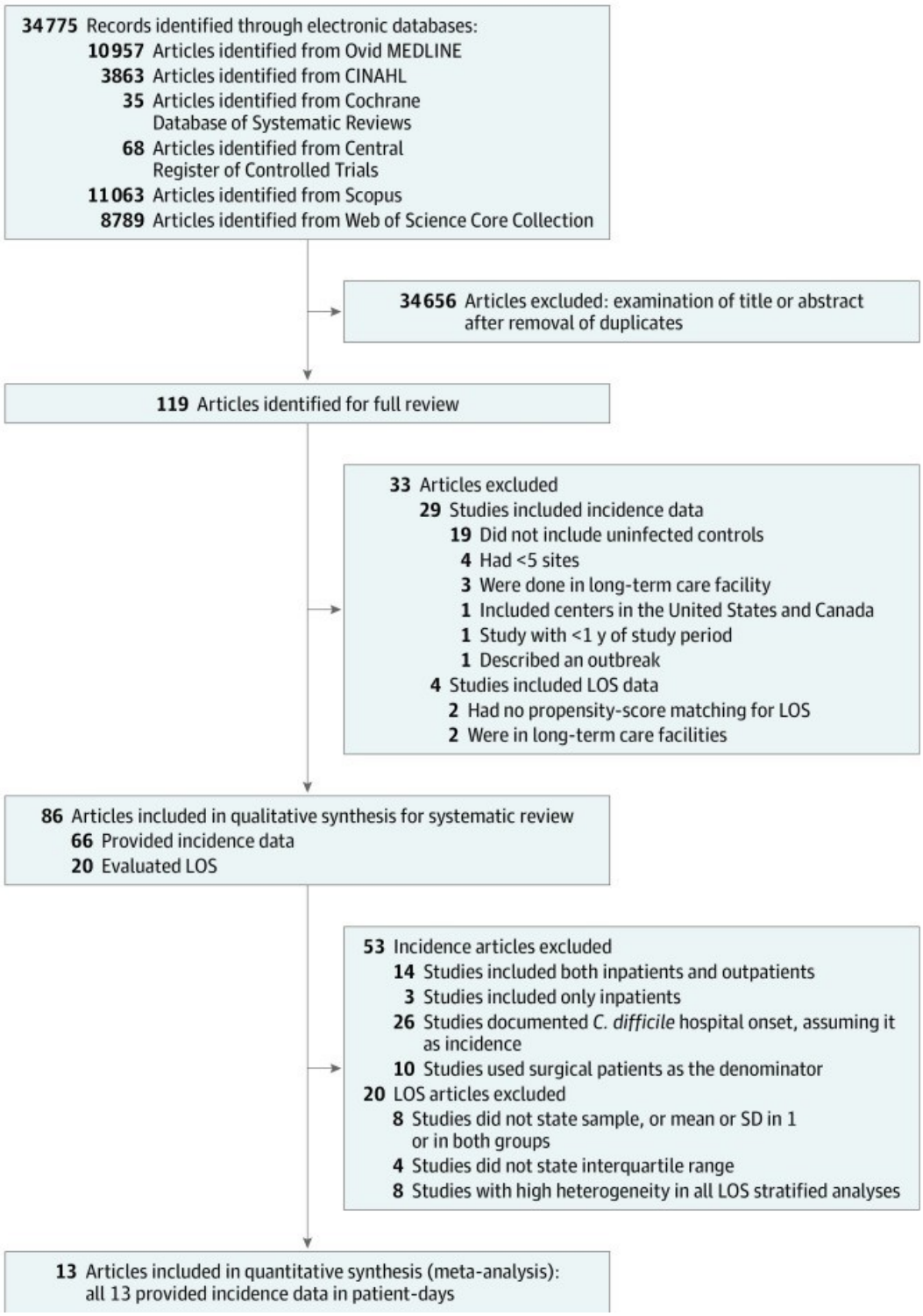
103. Kufelnicka AM, Kirn TJ. Effective utilization of evolving methods for the laboratory diagnosis of *Clostridium difficile* infection. Clin Infect Dis. 2011;52(12):1451-1457. doi:10.1093/cid/cir201 [PubMed: 21628487] [CrossRef: 10.1093/cid/cir201]

104. Thompson ND, Edwards JR, Dudeck MA, Fridkin SK, Magill SS. Evaluating the use of the case mix index for risk adjustment of healthcare-associated infection data: an illustration using *Clostridium difficile* infection data from the National Healthcare Safety Network. Infect Control Hosp Epidemiol. 2016;37(1):19-25. doi:10.1017/ice.2015.252 [PMCID: PMC6498436] [PubMed: 26486597] [CrossRef: 10.1017/ice.2015.252]

105. Goto M, Ohl ME, Schweizer ML, Perencevich EN. Accuracy of administrative code data for the surveillance of healthcare-associated infections: a systematic review and meta-analysis. Clin Infect Dis. 2014;58(5):688-696. doi:10.1093/cid/cit737 [PubMed: 24218103] [CrossRef: 10.1093/cid/cit737]

Figures and Tables

Figure.



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Literature Search for Articles That Evaluated Incidence and Length of Stay (LOS) Associated With *Clostridium difficile* Infection

CINAHL indicates Cumulative Index of Nursing and Allied Health.

Table 1.

Multicenter Studies (≥5 Sites) That Evaluated *Clostridium difficile* Infection Incidence Calculated Using Patient-Days

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Abbreviations: CDC, Centers for Disease Control and Prevention; HCF, health care facility; HO, hospital onset; *ICD-9*, *International Classification of Diseases, Ninth Revision*; Q, quarter.

Table 2.

Multicenter Studies (≥5 Sites) That Evaluated *Clostridium difficile* Infection Incidence Calculated Using Person-Years

Open in a separate window

Abbreviations: AHRQ, Agency for Healthcare Research and Quality; CDI, *Clostridium difficile* infection; *ICD-9*, *International Classification of Diseases, Ninth Revision*; VHA, Veterans Health Administration.

Table 3.

Multicenter Studies (≥5 Sites) That Evaluated *Clostridium difficile* Infection Incidence Using Incident Cases

Open in a separate window

Abbreviations: AHRQ, Agency for Healthcare Research and Quality; CDI, *Clostridium difficile* infection; HO, hospital onset; *ICD-9*, *International Classification of Diseases, Ninth Revision*; NHDS, National Hospital Discharge Survey; NIS, National Inpatient Sample; VA, Veterans Affairs.

Table 4.

Length of Stay Associated With *Clostridium difficile* Infection Among Studies That Used Appropriate Methods[a]

Open in a separate window

Abbreviations: AHRQ, Agency for Healthcare Research and Quality; CDI, *Clostridium difficile* infection; HCF, health care facility; HO, hospital onset; *ICD-9*, *International Classification of Diseases, Ninth Revision*; IQR, interquartile range; LOS, length of stay; NIS, National Inpatient Sample; VA, Veterans' Affairs.

[a]Methods include propensity score matching or postinfection LOS or matched on preinfection LOS or multistate modeling.
[b]The Downs and Black scale measures study quality, with a score of 18 or higher indicating higher quality, and a maximum score of 28 possible.[10]